Tetrahedron Letters 51 (2010) 4354–4356

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Green, catalyst-free thioacetalization of carbonyl compounds using glycerol as recyclable solvent

Gelson Perin [a,*], Luzia G. Mello [a], Cátia S. Radatz [a], Lucielli Savegnago [b], Diego Alves [a], Raquel G. Jacob [a], Eder J. Lenardão [a]

[a] *Instituto de Química e Geociências, LASOL, Universidade Federal de Pelotas, UFPel, 96010-900 Pelotas, RS, Brazil*
[b] *Universidade Federal do Pampa, UNIPAMPA, Campus de Uruguaiana, BR 472, Km 7, Uruguaiana, RS, Brazil*

ARTICLE INFO

Article history:
Received 13 May 2010
Revised 2 June 2010
Accepted 11 June 2010
Available online 19 June 2010

Keywords:
Glycerol
Thioacetals
Green chemistry

ABSTRACT

We describe herein the use of glycerol as an efficient and a recyclable solvent in the thioacetalization of aldehydes and ketones. The catalyst-free reactions proceed easily using glycerol at 90 °C and the corresponding thioacetals were obtained in good to excellent yields. Glycerol was recovered and utilized for further thioacetalization reactions.

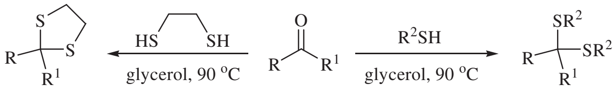
The protection of carbonyl groups as thioacetals is a general and a popular protocol in organic chemistry[1] and is frequently used as a synthetic step for the preparation of many important natural/unnatural organic compounds.[2] Thioacetals are useful carbonyl-protecting groups, thanks to their inherent stability under both acidic and basic conditions.[1] Commonly, these compounds are prepared by the reaction of carbonyl compounds with thiols or dithiols catalyzed by protic and Lewis acids,[3] such as HCl[3a] and PTSA,[3b] $BF_3\cdot OEt_2$,[3c] $AlCl_3$,[3d] $TiCl_4$,[3e] $TeCl_4$,[3f] $LaCl_3$,[3g] $SiCl_4$,[3h] $(CH_3)_3SiCl$,[3i] $SOCl_2$–SiO_2,[3j] LiBr,[3k] $InCl_3$,[3l] molecular I_2,[3m] NBS,[3n] and selenonium ionic liquid.[3o] Unfortunately, the majority of these protocols have certain disadvantages, such as the requirement for stoichiometric amounts of catalysts, the use of expensive reagents and/or toxic chlorinated organic solvents and, in most of the cases, the harsh reaction condition.[3]

In this context, the choice of the solvent is a crucial step in a chemical reaction. The development of green solvents from renewable resources has gained much interest recently because of the extensive uses of solvents in almost all of the chemical industries, and of the predicted disappearance of fossil oil.[4] The wanted characteristics for a green solvent include no flammability, high availability, obtaining from renewable sources, and biodegradability.[5] With the increase in biodiesel production world-wide, the market saturation of glycerol, a side product of biodiesel production, is inevitable.[6] The use of glycerol as a promising medium for organic reactions was recently demonstrated by us[7] and others.[8] These include Pd-catalyzed Heck[8a–c] and Suzuki[8a] cross-couplings, base-[8b] and acid-[7a] promoted condensations, catalytic hydrogenation,[8c,d] and asymmetrical reduction.[8c]

The peculiar physical and chemical properties of glycerol, such as polarity, low toxicity, biodegradability, high boiling point, and ready availability from renewable feed stocks,[9] prompted us to extend its use as a green solvent in organic synthesis. In this sense, we describe here the catalyst-free synthesis of thioacetals using glycerol as a solvent (Scheme 1).

Firstly, we reacted benzaldehyde **1a** and benzenethiol **2a** using glycerol as solvent at different temperatures to optimize the reaction conditions to access the thioacetal **3a**. When the reactions were performed both at room temperature and at 60 °C, **3a** was formed in poor yields. To our satisfaction, by increasing the temperature to 90 °C the reaction proceeds smoothly, furnishing thioacetal **3a** in excellent yield (Table 1; entry 1). In an optimized reaction, benzaldehyde **1a** (1.0 mmol) was dissolved in glycerol (3 mL) and reacted with benzenethiol **2a** (2.0 equiv) at 90 °C during 3.5 h, yielding **3a** in 96% yield (Table 1).[10]

To explore the scope and limitations of this new protocol, a range of aromatic and aliphatic aldehydes and ketones with



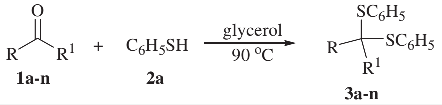
Scheme 1.

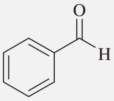
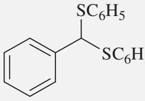
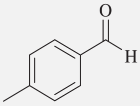
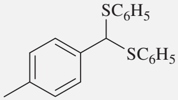
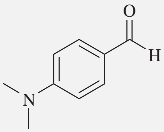
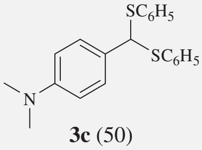
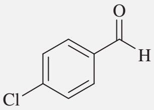
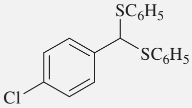
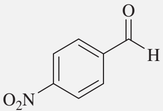
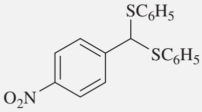
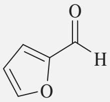
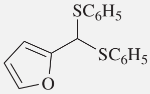
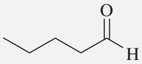
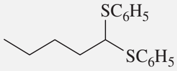
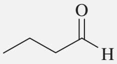
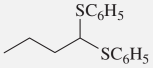
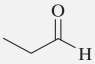
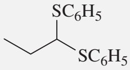
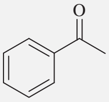
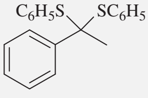
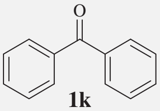
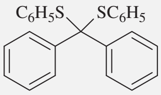
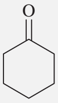
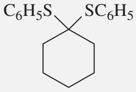
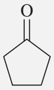
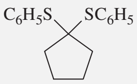
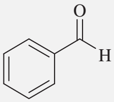
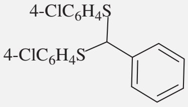
---

[*] Corresponding author. Tel./fax: +55 5332757354.
E-mail addresses: gelson_perin@ufpel.edu.br, perin@pq.cnpq.br (G. Perin).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.06.049

Table 1
Reaction of benzenethiol **2a** with carbonyl compounds **1a–n** in glycerol[a]



Entry	Carbonyl compound	Time (h)	Product yield[b] (%)
1	 **1a**	3.5	 **3a** (96)
2	 **1b**	8.0	 **3b** (94)
3	 **1c**	18.0	 **3c** (50)
4	 **1d**	6.0	 **3d** (96)
5	 **1e**	7.0	 **3e** (89)
6	 **1f**	2.0	 **3f** (76)
7	 **1g**	4.0	 **3g** (75)
8	 **1h**	3.5	 **3h** (65)
9	 **1i**	3.0	 **3i** (80)
10	 **1j**	12.0	 **3j** (80)
11	 **1k**	11	 **3k** (78)
12	 **1l**	9.5	 **3l** (97)
13	 **1m**	8.0	 **3m** (98)
14[c]	 **1a**	4.5	 **3n** (90)

[a] Reactions performed in the presence of carbonyl compound (1 mmol), benzenethiol (2.0 mmol) in glycerol (3 mL) at 90 °C.
[b] Yields are given for isolated products. The compounds were identified by mass spectrometry, ^{1}H, and ^{13}C NMR and compared with the literature data.[3]
[c] 4-Chlorobenzenethiol (2.0 mmol) was used.

various substitution patterns were reacted with benzenethiol **2a** under the optimized conditions. As can be seen from Table 1, most of the substrates gave good yields of the corresponding thioacetals.

Except for *p*-(*N*,*N*-dimethyl)-benzaldehyde **1c** (Table 1; entry 3), all the aromatic aldehydes containing electron-donating or electron-withdrawing groups gave good yields of the corresponding products (Table 1; entries 2, 4, and 5).

Heteroarylaldehyde **1f** yielded thioacetal **3f** in 76% yield after 2 h (Table 1; entry 6). Thioacetals **3g–i** were obtained in satisfactory yields starting from the parent alkyl aldehydes **1g–i** after stirring for 3–4 h (Table 1; entries 7–9). When 4-chlorobenzenethiol was used instead of **2a** in the reaction with benzaldehyde, the corresponding thioacetal **3n** was obtained in excellent yield after 4.5 h (Table 1; entry 14). Not only aldehydes **1a–i** but also ketones **1j–m** reacted very smoothly using glycerol as the solvent. Thus, bis-aryl, alkyl-aryl, and cyclic ketones reacted with benzenethiol **2a** and the respective products **3j–m** were obtained in satisfactory yields but longer reaction times (Table 1; entries 10–13). Similar to the conventional, acid-catalyzed thioacetalizations, aldehydes were more reactive than ketones, except for substituted aromatic aldehydes **1b–e** (Table 1, entries 2–5).

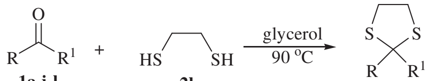
To expand the synthetic scope of this protocol, we carried out the reaction using 1,2-ethanedithiol **2b**. The results revealed that the reaction worked well using benzaldehyde, acetophenone, benzophenone, and cyclohexanone, furnishing the corresponding 1,3-dithiolanes **3o–r** in good yields (Table 2; entries 1–4).

In order to explore the ability of glycerol act as a selective solvent, we carried out a competitive thioacetalization reaction using an equimolar mixture of benzaldehyde **1a** (1.0 mmol) and acetophenone **1j** (1.0 mmol) with benzenethiol **2a** (2.0 mmol) (Scheme 2). After 12 h of reaction, a mixture of thioacetal **3a**, derived from benzaldehyde and **3j**, derived from acetophenone, was isolated in 96% yield and in a **3a**/**3j** ratio = 97:3.

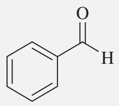
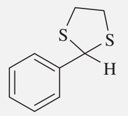
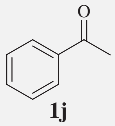
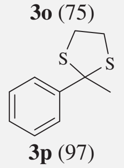
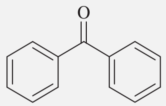
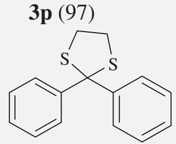
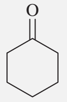
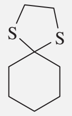
A reuse study of the glycerol was carried out for the reaction showed in Table 3.[11]After completion of thioacetalization, the reaction mixture was diluted with hexanes and the product was isolated. After complete removal of residual hexanes, the glycerol was directly reused for further reactions. Glycerol maintained its good level of efficiency even after being reused four times (Table 3). The product **3a** was obtained in 96%, 96%, 96%, 94%, and 90% yields after successive cycles. The effect of the presence of water in the yield of **3a** was verified using a mixture glycerol/water (97:3) as the solvent. In this case, the product **3a** was obtained only in 25% yield after 5 h.

In summary, glycerol has proved to be an efficient and recyclable solvent for the catalyst-free thioacetalization of aldehydes and ketones. The reactions proceed easily using low-cost and

Table 2
Reaction of 1,2-ethanedithiol **2b** with carbonyl compounds[a]

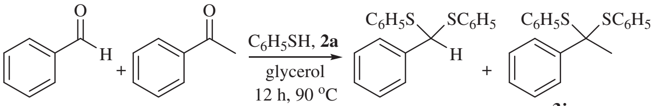


1a,j-l **2b** **3o-r**

Entry	Carbonyl compound	Time (h)	Product yield (%)[b]
1	 **1a**	4.0	 **3o** (75)
2	 **1j**	18.0	 **3p** (97)
3	 **1k**	16.0	 **3q** (83)
4	 **1l**	11.5	 **3r** (85)

[a] Reactions performed in the presence of carbonyl compound (1 mmol), 1,2-ethanedithiol (1.0 mmol) in glycerol (3 mL) at 90 °C.

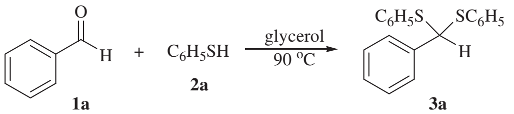
[b] Yields are given for isolated products. The compounds were identified by mass spectrometry, ^{1}H, and ^{13}C NMR and compared with the literature data.[3]



1a **1j** **3a** **3j**

Scheme 2.

Table 3
Reuse of glycerol in thioacetalization of benzaldehyde **1a**



1a **2a** **3a**

Run	Reaction time (h)	Yield **3a**[c] (%)
1[a]	3.5	96
2[b]	3.5	96
3[b]	3.5	96
4[b]	3.5	94
5[b]	5.0	90

[a] Reactions performed in the presence of benzaldehyde **1a** (1 mmol), benzenethiol **2a** (2.0 mmol) in glycerol (3 mL) at 90 °C.

[b] Recovered glycerol was used.

[c] Yields are given for isolated products.

renewable feedstock glycerol and the thioacetals were obtained in good to excellent yields. Glycerol can be easily recovered and utilized for further thioacetalization reactions and is particularly appropriate to the green chemistry concept. Applications of glycerol in other organic reactions are ongoing in our laboratory.

Acknowledgments

We are grateful to FAPERGS, FINEP, CAPES, and CNPq for the financial support.

References and notes

1. (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; (b) Kocienski, P. J. *Protecting Groups*; Stuttgart: Thieme, 1994; (c) Cordes, E. H.; Bull, H. G. *Chem. Rev.* **1974**, *74*, 581–603.
2. (a) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021–2040; (b) Smith, A. B., III; Condon, S. M.; McCauley, A. J. *Acc. Chem. Res.* **1998**, *31*, 35–46; (c) Mori, Y.; Kohchi, Y.; Suzuki, M. *J. Org. Chem.* **1991**, *56*, 631–637; (d) Oh, S.; Jeong, I. H.; Ahn, C. M.; Shin, W. S.; Lee, S. *Bioorg. Med. Chem.* **2004**, *12*, 3783–3790; (e) Rehnberg, N.; Magnusson, G. *J. Org. Chem.* **1990**, *55*, 4340–4349; (f) Tony, K. A.; Denton, R. W.; Dilhas, A.; Jiménez-Barbero, J.; Mootoo, D. R. *Org. Lett.* **2007**, *9*, 1441–1444; (g) Benda, K.; Regenhardt, W.; Schaumann, E.; Adiwidjaja, G. *Eur. J. Org. Chem.* **2009**, 1016–1021; (h) Smith, A. B., III; Adams, C. M. *Acc. Chem. Res.* **2004**, *37*, 365–377.
3. (a) Ralls, J. W.; Dobson, R. M.; Reigel, B. *J. Am. Chem. Soc.* **1949**, *71*, 3320–3325; (b) Djerassi, C.; Gorman, M. *J. Am. Chem. Soc.* **1953**, *75*, 3704–3708; (c) Nakata, T.; Nagao, S.; Mori, S.; Oishi, T. *Tetrahedron Lett.* **1985**, *26*, 6461–6464; (d) Ong, B. S. *Tetrahedron Lett.* **1980**, *21*, 4225–4428; (e) Kumar, V.; Dev, S. *Tetrahedron Lett.* **1983**, *24*, 1289–1292; (f) Tani, H.; Masumoto, K.; Inamasu, T. *Tetrahedron Lett.* **1991**, *32*, 2039–2042; (g) Garlaschelli, L.; Vidari, G. *Tetrahedron Lett.* **1990**, *31*, 5815–5816; (h) Ku, B.; Oh, D. Y. *Synth. Commun.* **1989**, *19*, 433–438; (i) Ong, B. S.; Chan, T. H. *Synth. Commun.* **1977**, *7*, 283–286; (j) Kamitori, Y.; Hojo, M.; Masuda, R.; Kimura, T.; Yoshida, T. *J. Org. Chem.* **1986**, *51*, 1427–1431; (k) Firouzabadi, H.; Iranpoor, N.; Karimi, B. *Synthesis* **1999**, 58–60; (l) Muthusamy, S.; Babu, S. A.; Gunanathan, C. *Tetrahedron Lett.* **2001**, *42*, 359–362; (m) Samajdar, S.; Basu, M. K.; Becker, F. F.; Banik, B. K. *Tetrahedron Lett.* **2001**, *42*, 4425–4427; (n) Kamal, A.; Chouhan, G. *Synlett* **2002**, 474–476; (o) Lenardão, E. J.; Borges, E. L.; Mendes, S. R.; Perin, G.; Jacob, R. G. *Tetrahedron Lett.* **2008**, *49*, 1919–1921.
4. (a) Handy, S. T. *Chem. Eur. J.* **2003**, *9*, 2938–2944; (b) Leitner, W. *Green Chem.* **2007**, *9*, 923; (c) Horváth, I. T. *Green Chem.* **2008**, *10*, 1024–1028; (d) Giovanni, I.; Silke, H.; Dieter, L.; Burkhard, K. *Green Chem.* **2006**, *8*, 1051–1055; (e) Clark, J. H. *Green Chem.* **1999**, *1*, 1–8. and references cited therein.
5. Nelson, W. M. *Green Solvents for Chemistry: Perspectives and Practice*; Oxford University Press: Oxford, 2003.
6. Johnson, D. T.; Taconi, K. A. *Environ. Prog.* **2007**, *26*, 338–348.
7. (a) Silveira, C. C.; Mendes, S. R.; Líbero, F. M.; Lenardão, E. J.; Perin, G. *Tetrahedron Lett.* **2009**, *50*, 6060–6063; (b) Lenardão, E. J.; Trecha, D. O.; Ferreira, P. C.; Jacob, R. G.; Perin, G. *J. Braz. Chem. Soc.* **2009**, *20*, 93–99; (c) Lenardão, E. J.; Silva, M. S.; Sachini, M.; Lara, R. G.; Jacob, R. G.; Perin, G. *ARKIVOC* **2009**, *xi*, 221–227.
8. (a) Wolfson, A.; Dlugy, C. *Chem. Pap.* **2007**, *61*, 228–232; (b) Wolfson, A.; Litvak, G.; Shotland, C.; Dlugy, Y.; Tavor, D. *Ind. Crops Prod.* **2009**, *30*, 78–81; (c) Wolfson, A.; Dlugy, C.; Shotland, Y. *Environ. Chem. Lett.* **2007**, *5*, 67–71; (d) Wolfson, A.; Dlugy, C.; Shotland, Y.; Tavor, D. *Tetrahedron Lett.* **2009**, *50*, 5951–5953; (e) He, F.; Li, P.; Gu, Y.; Li, G. *Green Chem.* **2009**, *11*, 1767–1773; (f) Karam, A.; Villandier, N.; Delample, M.; Koerkamp, C. K.; Douliez, J.-P.; Granet, R.; Krausz, P.; Barrault, J.; Jérôme, F. *Chem. Eur. J.* **2008**, *14*, 10196–10200; (g) Gu, Y.; Barrault, J.; Jérôme, F. *Adv. Synth. Catal.* **2008**, *350*, 2007–2012.
9. Pagliaro, M.; Rossi, M. In *The Future of Glycerol: New Usages for a Versatile Raw Material*; Clark, J. H., Kraus, G. A., Eds.; RSC Green Chemistry Series: Cambridge, 2008.
10. *General procedure for the thioacetalization reactions*: To a round-bottomed flask containing the appropriate carbonyl compound (1.0 mmol) and glycerol (3 mL) was added benzenethiol **2a** (2.0 mmol) or 1,2-ethanethiol **2b** (1.0 mmol). The reaction mixture was allowed to stir at 90 °C for the time indicated in Tables 1 and 2. After that, the reaction mixture was washed with hexanes (3 × 5 mL) and the upper organic phase was separated from glycerol, dried with $MgSO_4$, and evaporated under reduced pressure. The product was isolated by column chromatography using hexane or hexane/ethyl acetate as eluent. Selected spectral data for 1-(phenyl(phenylthio)methylthio)benzene[12] **3a**: Yield: 96%. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37–7.22 (m, 15H), 5.43 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.6, 134.5, 132.5, 128.8, 128.4, 128.0, 127.8, 127.7, 60.4.
11. *Reuse of glycerol*: To a round-bottomed flask containing benzaldehyde **1a** (1.0 mmol) and glycerol (3 mL) was added benzenethiol **2a** (2.0 mmol). The reaction mixture was allowed to stir at 90 °C for 3.5 h. After that, the reaction mixture was washed with hexanes (3 × 5 mL) and the upper organic phase was separated from glycerol. The product was isolated according to the procedure described above. The glycerol was dried under vacuum and reused for further reactions.
12. Wu, Y. C.; Zhu, J. *J. Org. Chem.* **2008**, *73*, 9522–9524.